



## **NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL**

### **A PROSPECTIVE EVALUATION OF THE RADIOGRAPHIC EFFICACY OF ETANERCEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS OR PSORIATIC ARTHRITIS**

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<b>Compound Name:</b>	Etanercept
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## 1. INTRODUCTION

Rheumatoid arthritis (RA) affects almost 1% of the population and is associated with rapid functional loss and reduced life expectancy. Disease remission and radiographic non-progression are goals of treatment of RA. For patients with RA, a variety of ‘conventional’ and novel biologic treatments (Disease Modifying Antirheumatic Drugs, DMARDs) are available. Numerous clinical trials and extensive post marketing surveillance have demonstrated the high efficacy and favorable safety profile of biologic drugs in comparison with traditional DMARDs.

Several randomized double blind clinical trials (COMET<sup>a</sup>, TEMPO<sup>b, c</sup>) have demonstrated the efficacy of Etanercept alone and in combination with methotrexate (MTX). Etanercept in combination with MTX reduced disease activity, slowed radiographic progression and improved function more effectively than either monotherapy. Furthermore, a statistically significant improvement of the Total Sharp Score (TSS) has been reported for the combination suggesting that regression of erosion may occur in some patients<sup>b, c, d</sup>.

Psoriatic Arthritis (PsA) is a chronic inflammatory disorder characterised by arthritis and psoriasis, variably associated with other extra-articular manifestations. It has traditionally been considered a milder and less disabling disease than RA, however this view has recently been challenged by a number of studies showing approximately 40% of patients with PsA develop joint erosion and damage<sup>e, f</sup>.

Several studies have demonstrated the efficacy of Etanercept versus placebo in reducing the signs and symptoms of PsA and psoriasis<sup>g, h</sup>. In addition, inhibition of radiological progression was demonstrated using a modification of the Sharp Score to include joints frequently affected in PsA<sup>h, i</sup>.

### 1.1. Background and Rationale

Randomized clinical trials evaluate efficacy in selective groups of patients defined by strict inclusion criteria. However, the value of these trials in predicting effectiveness in a "real world" situation may have limitations. Data from the German biologics register (RABBIT) which includes patients that are out-with routine practice, estimate that around 21-33% of patients included in the register would have been eligible for the major trials<sup>j</sup>. Thus patients recruited to such tightly controlled studies reflect only a proportion of the patient population treated with biologic agents in routine care.

It is known from the COMET trial that patients who start Etanercept in combination with MTX treatment early have a great chance of reaching clinical remission and radiographic non-progression than with MTX<sup>a</sup>. It is unclear however, how many patients with early arthritis achieve remission and radiographic non-progression under the conditions of routine rheumatologic care using local recommendations of Etanercept treatment (inadequate response to at least 2 DMARDs, one of which being MTX).

In addition, evidence suggests that radiographic progression may continue in patients receiving conventional treatment, even when clinical remission is achieved; the so-called ‘Silent Progressor’<sup>k, l, m</sup>.

This study aims to collect data on radiological progression and disease activity during routine use of Etanercept in RA and PsA in Germany.

Please refer to the [Product Label \(SMPC\)](#) for further information on Etanercept.

## **2. STUDY OBJECTIVES AND ENDPOINTS**

This is a non-interventional (NI), prospective, multi-center study to evaluate the radiological efficacy in patient with RA or PsA in routine treatment monitoring within a time interval of 12 to 18 months. Additionally, data of the disease activity in the same time window will be documented quarterly.

The radiological progression under Etanercept treatment will be compared to the radiological progression before Etanercept therapy in the same patient. Therefore, radiographs that were made in the patient’s history 12-48 months before treatment with Etanercept will be collected.

Patients with one existing radiograph of hands and feet (< 6 weeks prior to Etanercept treatment) and optional one or more existing radiographs taken in patient’s history 12 – 48 months before treatment with Etanercept will be recruited. According to the German recommendations for patients treated with biologics, the biologic therapy will be monitored by annually recorded radiographs. If available, these images will be collected in this NI trial.

### **2.1. Endpoints**

#### **2.1.1. Primary Endpoint:**

- a. Change in Radiographic Progression, measured by the “van der Heijde Sharp Score” for patients with RA<sup>n</sup>.
- b. Change in Radiographic Progression measured by the “PsA scoring method based on the Sharp Scoring Method of RA” for patients with PsA<sup>o</sup>.

#### **2.1.2. Secondary Endpoints:**

- c. Relationship between radiographic progression and disease duration.
- d. Comparison between radiographic progression before and under treatment with Etanercept.
- e. Change of Hannover Functional Ability Questionnaire (Funktionsfragebogen Hannover) (FFbH) (Appendix 5).
- f. Change of Disease Activity Score (DAS) (RA patients only) (Appendix 4).

- g. Assessment of involved body surface area (BSA) (PsA patients only)
  - a. *Estimation of BSA affected by psoriasis may be done by using hand palm area, which represents approximately 1% of total body surface.*

### 3. STUDY DESIGN

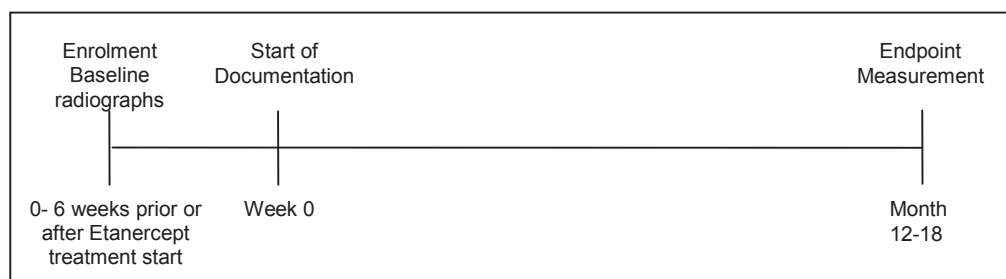
This is an NI, prospective, multi-center study to evaluate the safety and radiological efficacy in patient with RA or PsA in routine treatment monitoring within a time interval of 12 to 18 months. Additionally, data on disease activity in the same time window will be documented quarterly.

Patients with one existing radiograph of hands and feet (< 6 weeks prior or after Etanercept treatment) and one planned consecutive radiograph of hand and feet taken over 12 to 18 months will be recruited, according to German recommendations for patients treated with biologics.

Additionally, one historic radiograph should be collected if available, during a period of 12 to 48 months prior to start of treatment with Etanercept. This is optional.

The recruitment period will be 18 months' duration. The overall study will be 36 months' duration.

**Figure 1. Study Design**



### 4. STUDY POPULATION

All subjects enrolled should meet the usual prescribing criteria for Etanercept as per the local product information and should be entered into the study at the treating physician's discretion.

#### 4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study is a requirement for inclusion into this study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
- Definitive diagnosis of RA or PsA.
- Biologic naïve.
- Eligible for Etanercept treatment according to [Summary of Product Characteristics \(SmPC\)](#).
- Age  $\geq$  18 years.
- One plain radiograph of hands and feet (Anteroposterior) within 6 weeks prior to initiation of treatment with Etanercept and one planned consecutive radiograph of hand and feet taken over 12 to 18 months according to German recommendations for patients treated with biologics.

#### **4.2. Exclusion Criteria**

Subjects with any of the following conditions or characteristics will be excluded from study enrollment:

1. Age  $<$ 18 years at time of consent.
- Receipt of any investigational drug within 3 months of study inclusion.
  - Exclusion Criteria according to the Enbrel<sup>®</sup> SmPC, with particular attention to:
    - Hypersensitivity to the active substance (etanercept) or to any of the excipients.
    - Sepsis or risk of sepsis.
    - Active infections, including chronic or localised infections.
  - Subjects who have received any previous treatment with etanercept or other TNF $\alpha$  inhibitors or biologic agents
  - Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

## 5. STUDY TREATMENT AND DURATION

The use and dosage recommendations for Etanercept will take place on the basis of the approved [Product Label / SmPC](#) and will be adjusted solely according to medical and therapeutic necessity.

Patients will be observed for a period up to 18 months following initiation of Etanercept. Patients will complete the study either following planned radiological monitoring between 12 and 18 months or after 18 months following initiation of Etanercept.

## 6. STUDY PROCEDURES

The primary objective of this NI study is to evaluate the radiographic progression under practice conditions in a time interval of 12 to 18 months in patients with RA or PsA.

In Germany, radiographs are being routinely taken to document the course of the rheumatic disease and to guide on therapy decisions. The quality of radiographs must be standardised among the participating rheumatologists. The standard x-ray positioning for hands and feet is as follows:

- h. The hands are to be imaged separately on a single 18x24 film.
- i. Optimized positioning of the hands (wrist and forearm flat on the table/cassette).
- j. Hands centered horizontally on the half of the cassette to be exposed so that the metacarpo-phalangeal joints are midline and the position of the central ray vertically between the 2<sup>nd</sup> and 3<sup>rd</sup> metacarpo-phalangeal joints.
- k. X-ray of the feet sedentary, both feet on a 18x24 film flat on the cassette.

All radiographs will be checked for eligibility for reading by the rheumatologists and will then be sent to the external CRO. There, the radiographs will be digitalized if necessary, pseudonymized, and sent to readers who read the radiographs independently.

Additionally to the radiographic progression in the present observational trial the course of the disease of patients with RA or PsA resp. shall be documented by the treating physician.

Radiographs are collected at different time points:

- Visit 1: One plain radiograph of hands and feet (Anteroposterior) within 6 weeks prior to initiation of treatment with Etanercept (mandatory, inclusion criteria).
- Visit 1: Optional one historical radiograph of hands and feet (Anteroposterior) taken 12-48 months prior to initiation of treatment with Etanercept. If more than one radiograph has been taken in this time period, the earliest one will be collected.

Visit 5, 6 or 7: One plain radiograph of hands and feet (Anteroposterior) taken 12 – 18 months after initiation of treatment with Etanercept (not mandatory, only if available). The participation on the trial will end with the visit when the radiograph will be taken or, if no radiograph will be made, with visit 7.

During the course of the NI trial up to seven visits are planned: At the beginning of the survey (Visit 1), in the course of the treatment after 13 weeks (Visit 2), after 26 weeks (Visit 3), after 39 weeks (Visit 4) after 52 weeks (Visit 5), after 65 weeks (Visit 6) and after 78 weeks (Visit 7). If the second radiograph recommended by the German society of Rheumatology for the treatment with biologics will be taken in visit 5 (after 52 weeks) or visit 6 (after 65 weeks) the participation of the patient in this trial will end with this visit. Otherwise the participation will end with Visit 7. As this is an NI study the visit interval reflects the current practice and can be adjusted by the treating physician as needed.

### **6.1. Effectiveness criteria**

The efficacy of the treatment with Etanercept will be documented using, beside others, the following tools for the evaluation the course of the disease:

- l. Disease activity (DAS 28) (Appendix 4) including the Patient's Global Assessment (Appendix 1), number of swollen and tender joints and erythrocyte sedimentation rate.
- m. BSA for patients with PsA.
- n. Duration of morning stiffness (Appendix 3).
- o. Global assessment of disease activity by both physician and patient (Appendix 2, Appendix 1).
- p. C-reactive protein.
- q. Serum rheumatoid factor.
- r. Nail involvement for patients with PsA.

The physician receives a binder with clinical research forms for each patient where the data and findings of the patient are documented. With the exception of the not mandatory documentation of the previous radiograph the collection of data is prospective, i.e. the documentation of previous courses of treatment is not provided.

Dose and duration of treatment should be based on clinical and individual needs and are determined by the treating physician. To provide accurate information of the treatment, the initial Etanercept dose and all changes and the reasons for changes are documented during the course of the evaluation. The concomitant medication is determined by the treating physician and is registered in the documentation sheet.

## **6.2. Safety criteria**

In contrast to the usual procedure for clinical trials in observational trials no selection of patients at baseline is made. Thus, this study can provide new insights into the safety of Etanercept in the routine application. Therefore, all adverse events (AEs) that will occur during the observation period will be documented. Additionally, at the end of the observation both, the physician and the patient will be asked the general tolerability of the treatment with Etanercept and reasons for premature discontinuation rates will be analyzed.

## **6.3. Health Outcomes**

As a main issue of this evaluation it shall be measured how many patients that will achieve radiographic remission (non-progression) also achieve functional remission according to the Hannover Functional Ability Questionnaire (FFbH) (Appendix 5). In addition, the health-related quality of life will be measured using the EQ-5D questionnaire (Appendix 6).

The analysis of the relationship between the duration of the disease and the radiographic progression before and under treatment with Etanercept is of special interest and will be analyzed.

A proportion of the German patients treated with Etanercept in routine practice participate on a special patient care program, called RUDI & PIT. In this program the patients will be educated on certain topics around the drug Etanercept like e.g. administration, storage or cooling of the drug to enhance the adherence to therapy. It will be analyzed if participation on this program will influence health outcomes parameters like Quality of Life or treatment discontinuation rates.

## **6.4. Optional (12 to 48 months prior to initiation of Etanercept).**

## **6.5. The required Baseline Visit**

- s. Informed Consent.
- t. Medical History including primary disease (RA, PsA) duration since diagnosis.
- u. Demography.
- v. Inclusion/ Exclusion criteria according to protocol and SmPC.
- w. Prior drug treatment of primary diagnosis (RA or PsA).
- x. Concomitant drug treatment.
- y. Physical examination.
- z. Erythrocyte sedimentation rate (ESR).
- aa. C-reactive protein (CRP).

- bb. Serum rheumatoid factor (SRA).
- cc. Cyclic Citrullinated Protein (CCP).
- dd. Documentation of co-morbidities.
- ee. Number of swollen and tender joints.
- ff. Morning Stiffness (Appendix 3).
- gg. Patient's Global Assessment Appendix 1).
- hh. Physician's Global Assessment (Appendix 2).
- ii. Pain Visual Analogue Scale (VAS) (Appendix 7).
- jj. Assessment of involved BSA (PsA patients only).
- kk. Involvement of nails (PsA patients only).
- ll. Dactylitis (PsA patients only).
- mm. Hannover Functional Ability Questionnaire (FFbH) (Appendix 5).
- nn. EQ-5D Appendix 6).
- oo. Participation at the RUDI & PIT Compliance Program.
- pp. Required pre-treatment radiographs (within 6 weeks of treatment initiation) available or obtained.
- qq. Additional 'historic' radiographs collected 12 to 48 months prior to initiation of Etanercept treatment (optional). Radiographs must meet the standards of the protocol attached in Appendix 8 and are quality checked by the treating physician.

## **6.6. Study Period**

### **6.6.1. Scheduled Visits 2-6**

**[Visit 2/week 13; Visit 3/week 26; Visit 4/week 39; Visit 5/week 52; Visit 6/week 65]**

- rr. Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).
- ss. ESR.
- tt. CRP.
- uu. AEs.



vv. Number of swollen and tender joints.

ww. Morning Stiffness (Appendix 3).

xx. Patient's Global Assessment (Appendix 1).

yy. Physician's Global Assessment (Appendix 2).

zz. VAS (Appendix 7).

aaa. Assessment of involved BSA (PsA patients only).

bbb. Involvement of nails (PsA patients only).

ccc. Dactylitis (PsA patients only).

ddd. Hannover Functional Ability Questionnaire (FFbH) Appendix 5).

eee. EQ-5D (Appendix 6).

#### **6.6.2. Final (or close out) Visit 7/week 78**

fff. Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).

ggg. ESR.

hhh. CRP.

iii. SRA.

jjj. CCP.

kkk. AEs.

lll. Number of swollen and tender joints.

mmm. Morning Stiffness (Appendix 3).

nnn. Patients Global Assessment (Appendix 1).

ooo. Physicians Global Assessment (Appendix 2).

ppp. Pain VAS (Appendix 7).

qqq. Assessment of involved BSA (PsA patients only).

rrr. Involvement of nails (PsA patients only).

sss. Dactylitis (PsA patients only)

ttt. Hannover Functional Ability Questionnaire (FFbH) (Appendix 5).

uuu. EQ-5D (Appendix 6).

vvv. Plain Radiographs, hands and feet (Appendix 8).

### **6.7. Follow-up Visit**

A follow up assessment will take place only for those patients with an ongoing treatment-related AE at the end of the study period. The follow up will be scheduled approximately 28 days following the end of study and can be done by phone.

### **6.8. Subject Withdrawal**

Subjects experiencing AEs as listed in the Etanercept [SmPC](#) (with particular attention paid to Sections 4 (Contraindications), 5 (Special Warnings and 6 (Precautions) should be monitored and if indicated, treatment should be withdrawn according to provision of the [SmPC](#).

## 6.9. Schedule of Activities

Study Week <sup>11</sup> Visit Number	Baseline (Enrollment) 1	Week 13 2	Week 26 3	Week 39 4	Week 52 5	Week 65 6	Week 78 7
Informed Consent	x						
Anamnesis / Medical History	x						
Demographic data	x						
Inclusion/exclusion criteria	x						
<b>Treatment/Medication</b>							
Prior drug treatment	x						
Concomitant drug treatment	x	x	x	x	x	x	x
Safety							
Physical examination	x						
Inflammatory markers	x	x	x	x	x	x	x
Documentation of Comorbidities	x						
Documentation of AE		x	x	x	x	x	x
<b>Efficacy</b>							
Number of swollen and tender joints	x	x	x	x	x	x	x
Morning stiffness	x	x	x	x	x	x	x
Patients Global Assessment	x	x	x	x	x	x	x
Physicians Global Assessment	x	x	x	x	x	x	x
Pain VAS	x	x	x	x	x	x	x
<i><b>Additionally for PsA-patients</b></i>							
BSA of psoriatic skin	x	x	x	x	x	x	x
Nail involvement	x	x	x	x	x	x	x
Dactylitis	x	x	x	x	x	x	x
<b>Health Outcomes</b>							
Hannover Functional Ability Questionnaire (FFbH)	x	x	x	x	x	x	x
EQ-5D	x	x	x	x	x	x	x
Participation at the Etanercept compliance Program (Rudi Pit)	x						
<b>Radiologic/Radiology</b>							
<i><b>Mandatory radiograph</b></i>							

Study Week <sup>11</sup>	Baseline (Enrolment)	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78
Visit Number	1	2	3	4	5	6	7
1st picture not older than 6 weeks before 1st treatment with Etanercept	x						
<b>Optional radiographs</b>							
Optional: Historic picture, recorded between 12 and 48 month before 1st treatment with Etanercept	(x)						
<i>Documentation of Disease activity at the timepoint of the "historic" radiograph</i>							
Supportive therapy	(x)						
DAS 28	(x)						
Inflammatory markers	(x)						
Recording of a 2nd radiograph according to the recommendations of the German Society of Rheumatology. Earliest timepoint of this picture: 52 weeks after 1st treatment with Etanercept. After the second radiograph the final visit will be done. If radiograph not available from Week 52 to Week 78, the observational phase will end in Week 78.					(x)	(x)	(x)

## **7. DATA ANALYSIS/STATISTICAL METHODS**

The data collected and statistical methods proposed for analysis in this study will be documented in an NI Statistical Analysis Plan, which will be maintained by the sponsor. This plan will detail the interim analyses as well as the full analysis once the database is complete. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in an NI protocol amendment.

The intention-to-treat population will be used for all effectiveness analyses. It is defined as patients who received at least one dose of Etanercept. Missing values will be assumed to be missing at random and not imputed.

### **7.1. Sample Size Calculation**

This is an NI study and as such a formal sample size calculation is not required. However it is planned to enroll 1200 RA and approximately 300 PsA patients.

The change from baseline in radiographic progression (TSS) in RA subjects from the COMET<sup>1</sup> study based on a combination of MTX and Etanercept was 0.27 (standard deviation of 3.4) indicating that 1200 subjects would have 78% power at the 5% significance level.

For PsA, the Ravindran<sup>i</sup> paper indicates a mean yearly radiographic progression (modified TSS [mTSS]) of 2.85 with a standard deviation of 5.22. Sample size estimation based on this paper would indicate less than 100 subjects would be required to demonstrate this level of progression at >90% power and at the 5% significance level. It is anticipated that as many as 300 subjects with PsA may be included into the study.

### **7.2. Effectiveness Analysis**

The mean changes from baseline in the van der Heijde Sharp Score (TSS) (RA subjects only) will be summarised. The number and percentage of subjects with increase (>0.5), no change (-0.5 to 0.5) or decrease (<-0.5) in TSS will also be presented by visit. Subjects with no change or a decrease can be said to be in Radiographic remission.

The mean changes from baseline in the mTSS (PsA subjects only) will be summarised. The number and percentage of subjects with increase (>0.5), no change (-0.5 to 0.5) or decrease (<-0.5) in mTSS will also be presented by visit.

The change in the VAS from baseline will be summarised by visit.

The relationship between radiographic progression (TSS or mTSS) and disease duration will be assessed via a regression model with progression as the dependent variable and disease duration as the independent variable. Patients with RA and PsA will be analysed separately using data from the baseline visit (pre Etanercept radiograph). Additional covariates/factors

will be considered and documented in the Statistical Analysis Plan. These may include the following:

www. Radiographic progression prior to start of Etanercept (historical radiograph)

xxx. Patient's global assessment (Appendix 1).

yyy. Pain (VAS) (Appendix 7).

zzz. Hannover Functional Ability Questionnaire (FFbH) (Appendix 5)/

aaaa. Disease activity score (DAS 28) (RA patients) (Appendix 4).

bbbb. BSA (PsA patients).

A paired t-test will be performed on the TSS from before and after Etanercept treatment. The RA and PsA patients will be analysed separately. This will be performed on the TSS score from the pre Etanercept radiograph and the TSS from the 12-18 month radiograph (Visit 5, 6 or 7).

Physician (and Patient) Global Assessment of arthritis will be summarized by visit.

The FFbH will be summarised by visit. The number and percentage of subjects with functional remission will also be presented by visit.

The DAS-28 score (RA subjects only) will be summarized by visit.

BSA (PsA subjects only) will be summarized by visit.

The EQ-5D will be summarized by visit.

Duration of morning stiffness will be summarized by visit.

### **7.3. Safety Analysis**

Concomitant medications will be summarized. All AEs collected will be summarized. Any SAEs reported will be summarized.

### **7.4. Interim Analysis**

#### **7.4.1. First Interim analysis**

Data sets of est. 1000 patients (first visit, radiograph < 6 weeks before 1<sup>st</sup> visit and "historical" radiograph 12-48 months before first visit) will be eligible for statistical analysis at the beginning of 2013.

X-ray progression before treatment with Etanercept will be analyzed for potential confounding variables, e.g. disease duration, clinical outcome parameters and other disease characteristics like:

cccc. Patient's Global Assessment.

dddd. Pain (VAS).

eeee. FFbH.

ffff. Disease activity score (DAS 28) (RA patients).

gggg. BSA (PsA patients).

#### **7.4.2. Second Interim Analysis**

Complete data sets of est. 500 patients will be eligible for statistical analysis at the beginning of 2014.

X-ray progression before treatment with Etanercept will be analyzed for potential confounding variables, e.g. disease duration, clinical outcome parameters and other disease characteristics like:

hhhh. Patient's global assessment.

iiii. Pain (VAS).

jjjj. FFbH.

kkkk. Disease activity score (DAS 28) (RA-patients).

llll. BSA (PsA-patients).

### **8. DATA COLLECTION AND DATA MANAGEMENT**

#### **8.1. Case Report Forms (CRFs)**

A CRF should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The treating physician has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable,

complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the treating physician or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the treating physician's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## **8.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the treating physician agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the treating physician according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the treating physician becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another treating physician, another institution, or to an independent third party arranged by Pfizer. The treating physician must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **9. ADVERSE EVENT REPORTING**

### **9.1. Adverse Events (AEs)**

All observed or volunteered AEs regardless of treatment group (if applicable) or suspected causal relationship to Etanercept will be recorded on the AE page(s) of the CRF as follows.

For all AEs, the treating physician must pursue and obtain information adequate both to determine the outcome of the AEt and to assess whether it meets the criteria for classification as a serious adverse event (SAE) (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all AEs, sufficient information should be obtained by the treating physician to determine the causality of the



AE. The treating physician is required to assess causality. For AEs with a causal relationship to Etanercept, follow-up by the treating physician is required until the event or its sequelae resolve or stabilize at a level acceptable to the treating physician, and Pfizer concurs with that assessment.

## **9.2. Reporting Period**

For SAEs, the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent or signed data privacy statement, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the study drug within the observational period. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

## **9.3. Definition of an AE**

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- mmmm. Abnormal test findings;
- nnnn. Clinically significant symptoms and signs;
- oooo. Changes in physical examination findings;
- pppp. Hypersensitivity;
- qqqq. Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- rrrr. Drug overdose;
- ssss. Drug withdrawal;
- tttt. Drug abuse;
- uuuu. Drug misuse;
- vvvv. Drug interactions;
- www. Drug dependency;

xxxx. Extravasation;

yyyy. Exposure During Pregnancy;

zzzz. Exposure during breast feeding;

aaaaa. Medication Error.

#### **9.4. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

bbbbb. Test result is associated with accompanying symptoms, and/or

ccccc. Test result requires additional diagnostic testing or medical/surgical intervention, and/or

dddd. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

eeeee. Test result is considered to be an AE by the treating physician or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

#### **9.5. Serious Adverse Events**

An SAE is any untoward medical occurrence at any dose that:

ffff. Results in death;

ggggg. Is life-threatening (immediate risk of death);

hhhhh. Requires inpatient hospitalization or prolongation of existing hospitalization;

iiii. Results in persistent or significant disability/incapacity;

jjjjj. Results in congenital anomaly/birth defect.

Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or

result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### **9.5.1. Potential Cases of Drug-Induced Liver Injury**

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

kkkkk. Subjects with AST or ALT baseline values within the normal range who subsequently present with AST or ALT  $\geq 3$  times the upper limit of normal concurrent with a total bilirubin  $\geq 2$  times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase  $\geq 2$  times the upper limit of normal or not available.

lllll. Subjects with pre-existing AST or ALT baseline values above the normal range who subsequently present with AST or ALT  $\geq 2$  times the baseline values and  $\geq 3$  times the upper limit of normal, or  $\geq 8$  times the upper limit of normal (whichever is smaller) concurrent with a total bilirubin of  $\geq 2$  times the upper limit of normal and increased by one upper limit of normal over baseline or  $>3$  times the upper limit of normal (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase  $\geq 2$  times the upper limit of normal or not available.

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered). In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be

collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria A or B, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

## 9.6. Hospitalization

AEs reported from studies associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

mmmmm. Rehabilitation facilities;

nnnnn. Hospice facilities;

ooooo. Respite care (eg, caregiver relief);

ppppp. Skilled nursing facilities;

qqqqq. Nursing homes;

rrrrr. Routine emergency room admissions;

sssss. Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

ttttt. Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);

uuuuu. Social admission (eg, subject has no place to sleep);

vvvvv. Administrative admission (eg, for yearly physical exam);

wwwww. Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

xxxxx. Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

yyyyy. Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

### 9.7. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 9.8. Causality Assessment

The treating physician's assessment of causality must be provided for all AEs (serious and non-serious). The treating physician must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An treating physician's causality assessment is the determination of whether there exists a reasonable possibility that Etanercept caused or contributed to an AE. If the treating physician's final determination of causality is unknown and the treating physician does not know whether Etanercept caused the event, then the event will be handled as related to Etanercept for reporting purposes. If the treating physician's causality assessment is "unknown but not related to investigational product", this should be clearly documented in the CRF.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### 9.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

- a. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
- b. A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure during pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial EIU Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an EIU Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

zzzzz. “Spontaneous abortion” includes miscarriage and missed abortion;

aaaaa. All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure during pregnancy to the investigational medication should be reported.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

#### **9.10. Medication Error**

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

bbbbbb. Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

ccccc. Confusion with regard to invented name (eg, trade name, brand name).

The treating physician must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of whether an AE occurred:

ddddd. Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

eeeeee. Medication errors including potential medication errors or near misses that do not involve a patient directly. When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- b. An identifiable reporter;
- c. A suspect product;

- d. A medication error including potential medication error or near miss.

### 9.11. Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

fffff. Pregnancy exposure to a test article, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposure are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.

ggggg. Lactation exposure to a test article with or without an AE.

hhhhh. Overdose of a test article as specified in this protocol with or without an AE.  
Baby formula overdoses without any AEs are excluded.

iiiiii. Inadvertent or accidental exposure to a test article with or without an AE.

jjjjj. Amyotrophic lateral sclerosis

kkkkk. Demyelination and multiple sclerosis

lllll. Guillain-Barré Syndrome

mmmmm. Lymphoma

nnnnn. Mycosis fungoides;

ooooo. Cutaneous T-cell lymphoma;

ppppp. Progressive Multifocal Leukoencephalopathy (PML)

### 9.12. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs.

If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.



### **9.12.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of awareness of the event by the treating physician. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious AE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure during breast feeding and medication error cases.

In the rare event that the treating physician does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the treating physician is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the treating physician is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, a treating physician may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

### **9.12.2. Non-Serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

### **9.12.3. Sponsor Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

## **9.13. Communication of Issues**

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the treating physician is aware of any new information which might influence the evaluation of the benefits and risks of Etanercept, Pfizer should be informed immediately.

In addition, the treating physician will inform Pfizer immediately of any urgent safety measures taken by the treating physician to protect the study subjects against any immediate hazard, and of any serious breaches of this NI study protocol that the treating physician becomes aware of.

## **10. ETHICS**

### **10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

The IRB/IEC will review and approve the protocol before any subjects are enrolled.

### **10.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, such as the German Drug Law (AMG) and with the German BfArM-guideline for observation studies (Anwendungsbeobachtungen [AWB]) and local consensus recommendations, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers of America (PhRMA) guidelines and similar. The drug used is a marketed product and has to be prescribed according to German Drug Law AMG §67, 6. The patient will give written informed consent to the study. The IRB/IEC will review and approve the protocol before any subjects are enrolled.

### **10.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements as applicable.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The treating physician must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The treating physician, or a person designated by the treating physician, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The treating physician will retain the original of each subject's signed consent form.

## 11. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

### 11.1. Communication of results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on [ClinicalStudyResults.org](http://ClinicalStudyResults.org). Pfizer posts the results of studies that fall into either of the following categories:

qqqqqq. Studies that Pfizer registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) regardless of the reason for registration; OR

rrrrrr. All other studies for which the results have scientific or medical importance as determined by Pfizer.

Results are posted in two formats:

ssssss. The results of studies applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA) and/or An Act Regarding Advertising by Drug Manufacturers and Disclosure of Clinical Trials (state of Maine Reporting Requirements) are posted on [ClinicalTrials.gov](http://ClinicalTrials.gov) in a tabular format called Basic Results.

tttttt. The results of all required studies (even if not previously registered to ClinicalTrials.gov) and any voluntarily registered studies are posted on [ClinicalStudyResults.org](http://ClinicalStudyResults.org) in a format called a PhRMA website synopsis (PWS), the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

uuuuuu. For studies involving products already approved in any country and applicable under FDAAA and/or state of Maine, Pfizer posts results within one year of the primary outcome completion date (PCD). For all other studies that do not involve a Pfizer product, Pfizer posts results one year from last, subject last visit (LSLV);

vvvvvv. For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days after US regulatory approval or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

wwwwww. For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

### **11.2. Publications by treating physicians**

Pfizer has no objection to publication by treating physician of any information collected or generated by treating physician, whether or not the results are favorable to the study drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, treating physician will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Treating physician will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, treating physician agrees to delay the disclosure for a period not to exceed an additional 60 days.

Treating physician will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

As the Study is a multi-centre study, treating physician agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, treating physician is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Treating physicians, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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## Appendix 1. Sample Subject Global Assessment of Disease Activity

Please indicate your assessment of the overall activity of your rheumatoid arthritis by marking a vertical line at the appropriate position through the line below.

No  
disease  
activity



Extreme  
disease  
activity

## Appendix 2. Sample Physician Global Assessment of Disease Activity

Estimate the subject's disease activity over the last 2-3 days by marking a vertical line at the appropriate position through the line below.

No  
disease  
activity |-----| Extreme  
disease  
activity



### **Appendix 3. Sample Subject Morning Stiffness Worksheet**

The duration of morning stiffness should be determined by asking the following questions:

Over the last 2 days, when did you wake in the morning? \_\_\_\_\_

Over the last 2 days, when were you able to resume your normal activities without stiffness? \_\_\_\_\_

- ☐ Check this box if you were not able to resume your normal activities without stiffness (ie. your stiffness never went away – 24 hours of stiffness).

#### **Appendix 4. DAS28 Calculation**

In order to calculate the DAS28 the number of swollen joints and tender joints should be assessed using the 28 JOINT COUNT (tender28 and swollen28). The ESR should be measured (in mm/hour). In addition, the subject's general health measured on a VAS of 100 mm must be obtained. Using these data, the DAS28 can be calculated using the following formula:

$$\text{DAS28} = 0.56 * \text{sqrt}(\text{tender28}) + 0.28 * \text{sqrt}(\text{swollen28}) + 0.70 * \ln(\text{ESR}) + 0.014 * \text{VAS GH (general health)}$$

Joints assessed for the 28 joint count:

PIP 1 (right and left)

PIP 2 (right and left)

PIP 3 (right and left)

PIP 4 (right and left)

PIP 5 (right and left)

MCP 1 (right and left)

MCP 2 (right and left)

MCP 3 (right and left)

MCP 4 (right and left)

MCP 5 (right and left)

Wrists (right and left)

Elbows (right and left)


Shoulders (right and left)

Knees (right and left)

PIP = Proximal interphalangeal joint

MCP = Metacarpophalangeal joint

## Appendix 5. Funktionsfragebogen Hannover (FFbH)

Beobachtungsstudie Nr: B1801317  Patienten-Nummer

**FFbH – Funktionsfragebogen Hannover**

Geschlecht: ☐ männlich ☐ weiblich Geburtsdatum:       (TT/MM/JJ)

Visitendatum:       (TT/MM/JJ)

In den folgenden Fragen geht es um Tätigkeiten aus dem täglichen Leben. Bitte beantworten Sie jede Frage so, wie es für Sie im Moment (in Bezug auf die letzten 7 Tage) zutrifft und kreuzen Sie die entsprechende Zahl an.

Sie haben drei Antwortmöglichkeiten:

1 = Ja                      2 = Ja, aber mit Mühe                      3 = Nein oder nur mit fremder Hilfe


Sie können die Tätigkeit ohne Schwierigkeiten ausführen      Sie haben dabei Schwierigkeiten, z.B. Schmerzen, es dauert länger als früher oder Sie müssen sich dabei abstützen      Sie können es gar nicht oder nur, wenn eine andere Person Ihnen dabei hilft

1.	Können Sie Brot Streichen?	1	2	3
2.	Können Sie aus einem normal hohen Bett aufstehen?	1	2	3
3.	Können Sie mit der Hand Schreiben (mindestens eine Postkarte)?	1	2	3
4.	Können Sie Wasserhähne auf- und zudrehen?	1	2	3
5.	Können Sie sich strecken, um z.B. ein Buch von einem hohen Regal oder Schrank zu holen?	1	2	3
6.	Können Sie sich mindestens 10 kg schwere Gegenstände (z.B. einen vollen Wassereimer oder Koffer) hochheben und 10 Meter weit tragen?	1	2	3
7.	Können Sie sich von Kopf bis Fuß waschen und abtrocknen?	1	2	3
8.	Können Sie bücken und einen leichten Gegenstand (z.B. ein Geldstück oder zerknülltes Papier) vom Fußboden aufheben?	1	2	3
9.	Können Sie sich über einem Waschbecken die Haare waschen?	1	2	3
10.	Können Sie 1 Stunde auf einem ungepolsterten Stuhl sitzen?	1	2	3
11.	Können Sie 30 Minuten ohne Unterbrechung stehen (z.B. in einer Warteschlange)?	1	2	3
12.	Können Sie sich im Bett aus der Rückenlage aufsetzen?	1	2	3
13.	Können Sie Strümpfe an- und ausziehen?	1	2	3
14.	Können Sie im Sitzen einen kleinen heruntergefallenen Gegenstand (z.B. eine Münze) neben Ihrem Stuhl aufheben?	1	2	3
15.	Können Sie einen schweren Gegenstand (z.B. eine gefüllten Kasten Mineralwasser) vom Boden auf den Tisch Stellen?	1	2	3
16.	Können Sie sich einen Wintermantel an- und ausziehen?	1	2	3
17.	Können Sie ca. 100 Meter schnell laufen (nicht gehen), etwa um einen Bus zu erreichen?	1	2	3
18.	Können Sie öffentliche Verkehrsmittel (Bus, Bahn usw.) benutzen?	1	2	3

©FFbH

Wir bitten Sie, diesen Fragebogen vollständig auszufüllen und noch während Ihres heutigen Arztbesuches an Ihren Arzt zurückzugeben. Wir bedanken uns sehr für Ihre Mithilfe!

## Appendix 6. EQ-5D

Beobachtungsstudie Nr: B1801317  Patienten-Nummer

**Fragebogen zur Lebensqualität (EQ - 5D)**

Geschlecht: ☐ männlich ☐ weiblich Geburtsdatum:       (TT/MM/JJ)

Visitendatum:       (TT/MM/J J)

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

**Beweglichkeit / Mobilität**

Ich habe keine Probleme herumzugehen ☐

Ich habe einige Probleme herumzugehen ☐

Ich bin ans Bett gebunden ☐

**Für sich selbst sorgen**

Ich habe keine Probleme, für mich selbst zu sorgen ☐

Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen ☐

Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ☐

**Alltägliche Tätigkeiten (z.B. Arbeit, Studium, Hausarbeit, Familie- oder Freizeitaktivitäten)**

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ☐

Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ☐

Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ☐

**Schmerzen / Körperliche Beschwerden**

Ich habe keine Schmerzen oder Beschwerden ☐

Ich habe mäßige Schmerzen oder Beschwerden ☐

Ich habe extreme Schmerzen oder Beschwerden ☐

**Angst / Niedergeschlagenheit**

Ich bin nicht ängstlich oder deprimiert ☐

Ich bin mäßig ängstlich oder deprimiert ☐

Ich bin extrem ängstlich oder deprimiert ☐

Wir bitten Sie, diesen Fragebogen vollständig auszufüllen und noch während Ihres heutigen Arztbesuches an Ihren Arzt zurückzugeben. Wir bedanken uns sehr für Ihre Mithilfe!

## Appendix 7. Sample Patient Pain Visual Analog Scale

Indicate the amount of pain experienced during the last 2-3 days by marking a vertical line at the appropriate position through the line below.

No Pain |-----| Pain as bad as it could be

## Appendix 8. Radiographs

In Germany, radiographs are being routinely taken to document the course of the rheumatic disease and to guide on therapy decisions. The quality of radiographs must be standardised among the participating rheumatologists. The standard x-ray positioning for hands and feet is as follows:

xxxxxx. The hands are to be imaged separately on a single 18x24 film

yyyyyy. Optimized positioning of the hands (wrist and forearm flat on the table/cassette)

zzzzzz. Hands centred horizontally on the half of the cassette to be exposed so that the metacarpo-phalangeal joints are midline and the position of the central ray vertically between the 2<sup>nd</sup> and 3<sup>rd</sup> metacarpo-phalangeal joints

aaaaaaa. X-ray of the feet sedentary, both feet on a 18x24 film flat on the cassette

## Appendix 9. Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine transaminase
AMG	German Drug Law
AST	Aspartate transaminase
BSA	Body surface area
CCP	Cyclic citrullinated protein
CRF	Case Report Form
CRP	C-reactive Protein
CSR	Clinical Study Report
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drugs
EIU	Exposure in Utero
ESR	Erythrocyte sedimentation rate
FDAAA	Food and Drug Administration Amendments Act
FFbH	Funktionsfragebogen Hannover
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GPP	Good Pharmacoepidemiology Practices
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LSLV	Last subject, last visit
MCP	Metacarpophalangeal joint
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NI	Non-Interventional
PCD	Primary Completion Date
PhRMA	Pharmaceutical Research and Manufacturers of America
PIP	Proximal interphalangeal joint
PML	Progressive multifocal leukoencephalopathy
PsA	Psoriatic Arthritis
RA	Rheumatoid arthritis
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics
SRA	Serum rheumatoid factor
TSS	Total Sharp Score
VAS	Visual Analogue Scale



## 1. INTRODUCTION

The inclusion and exclusion criteria determined in the protocol from 20 September 2011, and the German translation from 01 October 2011, will be adapted according to the needs of medical practice. Firstly, the period of time between initiation of treatment with Etanercept and the plain radiograph of hands and forefeet will be expanded and secondly the inclusion of patients who were previously treated with a biologic agent will be included into this study.

The new inclusion and exclusion criteria are as followed:

### 4.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study is a requirement for inclusion into this study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
- Definitive diagnosis of RA or PsA.
- ~~Biologic naïve.~~
- Inclusion of subjects pretreated with other biologics other than Etanercept is possible
- Eligible for Etanercept treatment according to [Summary of Product Characteristics \(SmPC\)](#).
- Age  $\geq$  18 years
- One plain radiograph of hands and feet (Anteroposterior) within ~~6 weeks~~ 3 month prior to initiation of treatment with Etanercept and one planned consecutive radiograph of hand and feet taken over 12 to 18 months according to German recommendations for patients treated with biologics.



## 4.2 Exclusion Criteria

Subjects with any of the following conditions or characteristics will be excluded from study enrollment:

- Age <18 years at time of consent.
- Receipt of any investigational drug within 3 months of study inclusion.
- Exclusion Criteria according to the Enbrel® SmPC, with particular attention to:
  - Hypersensitivity to the active substance (Etanercept) or to any of the excipients.
  - Sepsis or risk of sepsis.
  - Active infections, including chronic or localised infections.
- Subjects who have received any previous treatment with Etanercept ~~or other TNF $\alpha$  inhibitors or biologic agents~~
- Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

## **2. RATIONAL FOR THE EXPANSION OF THE TIME PERIOD BETWEEN INITIATION OF ETANERCEPT TREATMENT AND GENERATION OF A RADIOGRAPH OF HAND AND FOREFEET**

Since the start of the study in March 2012 to August 2012 149 patients have been included. The study duration was calculated based on the assumption of a patient recruiting of 80-100 per month. According to statements by the attending physicians often the tight ceiling period between the X-ray and the initiation of treatment with Etanercept of 6 weeks is the main reason why patients cannot be included. In clinical practice a radiograph of the hands and feet is often taken due to the insufficient response to an existing therapy during a routine visit. At the subsequent visit, which usually takes place at intervals of 3 months, the decision to change the therapy is made.

Many clinical studies in the past 10 years show a radiographic progression in patients with rheumatoid arthritis or psoriatic arthritis under conventional DMARD therapy between 1.1 - 2.8 Sharp Score points per year (1.2). Under the assumption that, before initiation of treatment with Etanercept the radiographic progression is 2 points and under treatment with Etanercept 0, the mean inaccuracy by expanding the inclusion criteria of the distance between X-ray image and initiation of treatment with Etanercept from 6 weeks to 3 months

will be 0.12 points. This possible of error of 6% of the measured radiographic progression is acceptable.

### **3. RATIONAL FOR THE INCLUSION OF SUBJECTS PRE TREATED WITH OTHER BIOLOGICS**

Primary endpoints of the study are the change in radiographic progression in patients with rheumatoid arthritis and psoriatic arthritis treated with Etanercept. Evaluations of the Finnish register RobFin and a recent meta-analysis showed that patients treated with a 2nd TNF-antagonist after failure of a first anti-TNF can have a clinical response (3.4). The change in radiological progression under Etanercept treatment in subjects with an inadequate response to previous biological therapy has not been studied in clinical trials or in registries before. Therefore, it is useful, to include patients who were pre-treated with other biologics in the study to investigate the change in radiographic progression in these patients.

### **4. LITERATUR**

1) Two-Year Clinical and Radiographic Results With Combination Etanercept–Methotrexate Therapy Versus Monotherapy in Early Rheumatoid Arthritis

*Paul Emery, Ferdinand Breedveld, Desiree van der Heijde, Gianfranco Ferraccioli, Maxime Dougados, Deborah Robertson, Ronald Pedersen, Andrew S. Koenig, and Bruce Freundlich*

ARTHRITIS & RHEUMATISM

Vol. 62, No. 3, March 2010, pp 674–682

2) Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years.

*Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, Aletaha D, Matteson EL, Conaghan PG, Keystone E, van der Heijde D, Smolen JS.*

Ann Rheum Dis. 2011 Sep;70(9):1631-40. Epub 2011 Jun 27.

3) Outcomes of switching anti-TNF drugs in rheumatoid arthritis--a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN).

*Virkki LM, Valleala H, Takakubo Y, Vuotila J, Relas H, Komulainen R, Koivuniemi R, Yli-Kerttula U, Mali M, Sihvonen S, Krogerus ML, Jukka E, Nyrhinen S, Konttinen YT, Nordström DC*

Clin Rheumatol. 2011 Nov;30(11):1447-54. Epub 2011 Jun 7.

4) Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis.

*Rémy A, Avouac J, Gossec L, Combe B.*

Clin Exp Rheumatol. 2011 Jan-Feb;29(1):96-103. Epub 2011 Feb 23.



## 1. INTRODUCTION

In the protocol of 20 September 2011, and the German translation of 01 October 2011 (and its adaption regarding the EC-recommendations), a recruitment period of 18 months has been set. This was originally intended to last from March 2012 to the end of August 2013. During this period, 1,500 patients should be included in the study.

To achieve the planned number of patients the recruitment period is extended by 12 months. The new study design is shown below:

## 3. STUDY DESIGN

This is a NI, prospective, multi-center study to evaluate the safety and radiological efficacy in patient with RA or PsA in routine treatment monitoring within a time interval of 12 to 18 months. Additionally, data on disease activity in the same time window will be documented quarterly.

Patients with one existing radiograph of hands and feet (<3 month prior or after Etanercept treatment) and one planned consecutive radiograph of hand and feet taken over 12 to 18 months will be recruited, according to German recommendations for patients treated with biologics.

Additionally, one historic radiograph should be collected if available, during a period of 12 to 48 months prior to start of treatment with Etanercept. This is optional.

The recruitment period will be ~~18~~ 30 months' duration. The overall study will be ~~36~~ 48 months' duration.

## 2. RATIONAL FOR THE EXPANSION OF THE RECRUITMENT PERIOD

Since start of the study in March 2012 to end of May 2013 626 patients have been included. The design of the entire recruitment period of the study was based on the assumption that 80-100 patients will be enrolled per month. After the expansion of the inclusion and exclusion criteria in November 2012, the recruitment has already been improved to approximately 60 patients per month, but this was not sufficient to recruit the planned 1,500 patients by the end of August 2012.

If the current recruitment section will be maintained in the next months, an extension of the recruitment period for 12 months is required to achieve the planned number of patients. This also results in the extension of the overall study period.

## **1. INTRODUCTION**

In amendment 2 from 27 June 2013 a recruitment period of 30 months has been set. This was originally intended to last from March 2012 to the end of August 2014. According to the protocol from 20 September 2011, and the German translation from 01 October 2011 (and its adaption regarding the EC-recommendations) 1,500 patients should be included in the study during this period. The observation period was planned to last up to 18 month and should include the assessment of an optional radiograph taken 12 to 18 month after the start of Etanercept treatment.

To evaluate the long-term radiographic efficacy of Etanercept in patients with RA or PsA the observation period will be extended to 38 month. This includes the assessment of another optional radiograph taken 30 to 36 month after the start of Etanercept treatment, in accordance with the German recommendations for patients treated with biologics.

Based on experience from registries the number of recruited patients will be increase to 2,000 to ensure documentation over 12 month for 1,200 RA and 300 PsA patients.

The new study design is shown below:

## **2. STUDY OBJECTIVES AND ENDPOINTS**

This is a non-interventional (NI), prospective, multi-center study to evaluate the radiological efficacy in patient with RA or PsA in routine treatment monitoring within a time interval of 12 to 18 up to 36 months. Additionally, data of the disease activity in the same time window will be documented quarterly.

The radiological progression under Etanercept treatment will be compared to the radiological progression before Etanercept therapy in the same patient. Therefore, radiographs that were made in the patient's history 12-48 months before treatment with Etanercept will be collected.

Patients with one existing radiograph of hands and feet (< 3 months prior to or after start of Etanercept treatment) and optional one or more existing radiographs taken in patient's history 12 – 48 months before treatment with Etanercept will be recruited. According to the German recommendations for patients treated with biologics, the biologic therapy will be monitored by annually recorded radiographs. If available, these images will be collected in this NI trial.

## **3. STUDY DESIGN**

This is an NI, prospective, multi-center study to evaluate the safety and radiological efficacy in patient with RA or PsA in routine treatment monitoring within a time interval of 12 to 18 months. Additionally, data on disease activity in the same time window will be documented quarterly.



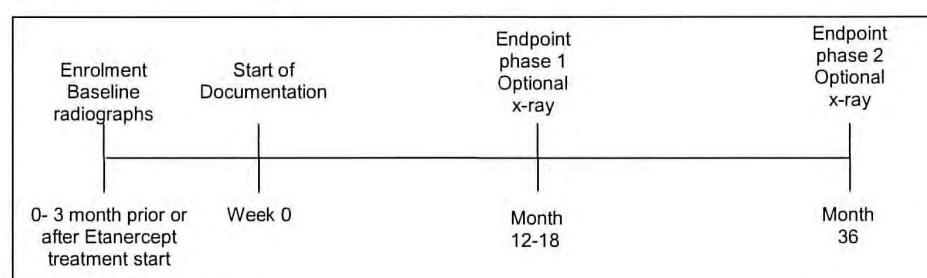
Patients with one existing radiograph of hands and feet (< 3 months prior to or after start of Etanercept treatment) and one planned consecutive radiograph of hand and feet taken over 12 to 18 months will be recruited, according to German recommendations for patients treated with biologics.

Additionally, one historic radiograph should be collected if available, during a period of 12 to 48 months prior to start of treatment with Etanercept. This is optional.

Concurrently disease activity data will be collected over ~~12 to~~ 18 month on a quarterly basis **and for further 18 month biannually.**

The recruitment period will be ~~30~~ **36** months' duration. The overall study will be ~~48~~ **72** months' duration.

**Figure 1. Study Design**



## 5. STUDY TREATMENT AND DURATION

The use and dosage recommendations for Etanercept will take place on the basis of the approved Product Label / SmPC and will be adjusted solely according to medical and therapeutic necessity.

Patients will be observed for a period up to ~~18~~ **36** months following initiation of Etanercept. Patients will complete the study ~~either following planned radiological monitoring between 12 and 18 months or after 18~~ **36** months following initiation of Etanercept.

## 6. STUDY PROCEDURES

The primary objective of this NI study is to evaluate the radiographic progression under practice conditions in a time interval of 12 to 18 months in patients with RA or PsA.

In Germany, radiographs are being routinely taken to document the course of the rheumatic disease and to guide on therapy decisions. The quality of radiographs must be standardised among the participating rheumatologists. The standard x-ray positioning for hands and feet is as follows:

- The hands are to be imaged separately on a single 18x24 film.
- Optimized positioning of the hands (wrist and forearm flat on the table/cassette).
- Hands centered horizontally on the half of the cassette to be exposed so that the metacarpo-phalangeal joints are midline and the position of the central ray vertically between the 2<sup>nd</sup> and 3<sup>rd</sup> metacarpo-phalangeal joints.
- X-ray of the feet sedentary, both feet on a 18x24 film flat on the cassette.

All radiographs will be checked for eligibility for reading by the rheumatologists and will then be sent to the external CRO. There, the radiographs will be digitalized if necessary, pseudonymized, and sent to readers who read the radiographs independently.

Additionally to the radiographic progression in the present observational trial the course of the disease of patients with RA or PsA resp. shall be documented by the treating physician.

Radiographs are collected at different time points:

- Visit 1: One plain radiograph of hands and feet (Anteroposterior) within 6 weeks prior to initiation of treatment with Etanercept (mandatory, inclusion criteria).
- Visit 1: Optional one historical radiograph of hands and feet (Anteroposterior) taken 12-48 months prior to initiation of treatment with Etanercept. If more than one radiograph has been taken in this time period, the earliest one will be collected.
- Visit 5, 6 or 7: One plain radiograph of hands and feet (Anteroposterior) taken 12 – 18 months after initiation of treatment with Etanercept (not mandatory, only if available). ~~The participation on the trial will end with the visit when the radiograph will be taken or, if no radiograph will be made, with visit 7.~~
- Visit 9, 10 One plain radiograph of hands and feet (Anteroposterior) taken 30 – 36 months after initiation of treatment with Etanercept (not mandatory, only if available).

During the course of the NI trial up to seven visits are planned: At the beginning of the survey (Visit 1), in the course of the treatment after 13 weeks (Visit 2), after 26 weeks (Visit 3), after 39 weeks (Visit 4) after 52 weeks (Visit 5), after 65 weeks (Visit 6), and after 78 weeks (Visit 7), **after 104 weeks (Visit 8), after 130 weeks (Visit 9) and after 156 weeks (Visit 10).** If the second radiograph recommended by the German society of Rheumatology for the treatment with biologics will be taken in visit 5 (after 52 weeks) or visit 6 (after 65 weeks) the participation of the patient in this trial will end with ~~this visit. Otherwise the participation will end with Visit 10~~ 7. As this is an NI study the



visit interval reflects the current practice and can be adjusted by the treating physician as needed.

#### **6.4 The required Baseline Visit**

- Informed Consent.
- Medical History including primary disease (RA, PsA) duration since diagnosis.
- Demography.
- Inclusion/ Exclusion criteria according to protocol and SmPC.
- Prior drug treatment of primary diagnosis (RA or PsA).
- Concomitant drug treatment.
- Physical examination.
- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Serum rheumatoid factor (SRA).
- Cyclic Citrullinated Protein (CCP).
- Documentation of co-morbidities.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patient's Global Assessment.
- Physician's Global Assessment.
- Pain Visual Analogue Scale (VAS) (.
- Assessment of involved BSA (PsA patients only).
- Involvement of nails (PsA patients only).
- Dactylitis (PsA patients only).
- Hannover Functional Ability Questionnaire (FFbH).
- EQ-5D.

- Participation at the RUDI & PIT Compliance Program.
- Required pre-treatment radiographs (within 6 weeks of treatment initiation) available or obtained.
- Additional 'historic' radiographs collected 12 to 48 months prior to initiation of Etanercept treatment (optional). Radiographs must meet the standards of the protocol attached in and are quality checked by the treating physician.

## **6.5 Study Period**

### **6.5.1 Scheduled Visits 2-6**

**[Visit 2/week 13; Visit 3/week 26; Visit 4/week 39; Visit 5/week 52; Visit 6/week 65]**

- Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).
- ESR.
- CRP.
- AEs.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patient's Global Assessment.
- Physician's Global Assessment.
- VAS.
- Assessment of involved BSA (PsA patients only).
- Involvement of nails (PsA patients only).
- Dactylitis (PsA patients only).
- Hannover Functional Ability Questionnaire (FFbH)
- EQ-5D.

### **6.5.2 ~~Final (or close-out)~~ Visit 7 (End of Phase 1)/week 78**

- Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).



- ESR.
- CRP.
- SRA.
- CCP.
- AEs.
- Number of swollen and tender joints.
- Morning Stiffness
- Patients Global Assessment.
- Physicians Global Assessment.
- Pain VAS.
- Assessment of involved BSA (PsA patients only).
- Involvement of nails (PsA patients only).
- Dactylitis (PsA patients only)
- Hannover Functional Ability Questionnaire (FFbH).
- EQ-5D.
- Plain Radiographs, hands and feet.

#### **6.5.3 Scheduled Visits 8/week 104**

- Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).
- ESR.
- CRP.
- AEs.
- Number of swollen and tender joints.
- Morning Stiffness.

- Patient's Global Assessment.
- Physician's Global Assessment.
- VAS.
- Assessment of involved BSA (PsA patients only).
- Involvement of nails (PsA patients only).
- Dactylitis (PsA patients only).
- Hannover Functional Ability Questionnaire (FFbH)
- EQ-5D.

#### **6.5.2 Scheduled Visit 9 and 10**

##### **[Visit 9/week 130; Visit 10/week 156]**

- Concomitant drug treatment including treatment of primary diagnosis (RA or PsA).
- ESR.
- CRP.
- SRA.
- CCP.
- AEs.
- Number of swollen and tender joints.
- Morning Stiffness.
- Patients Global Assessment.
- Physicians Global Assessment.
- Pain VAS.
- Assessment of involved BSA (PsA patients only).
- Involvement of nails (PsA patients only).

- Dactylitis (PsA patients only)
- Hannover Functional Ability Questionnaire (FFbH).
- EQ-5D.
- Plain Radiographs, hands and feet.

• **6.8 Schedule of Activities**

Visit Number	Baseline (Enrolment)	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78	Week 104	Week 130	Week 156
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>
Informed Consent										
Anamnesis / Medical History	x							x		
Demographic data	x									
Inclusion/exclusion criteria	x									
<b>Treatment/Medication</b>	x									
Prior drug treatment										
Concomitant drug treatment	x									
Safety	x	x	x	x	x	x	x	x	x	x
Physical examination	x									
Inflammatory markers	x	x	x	x	x	x	x	x	x	x
Documentation of Comorbidities	x									
Documentation of AE		x	x	x	x	x	x	x	x	x
<b>Efficacy</b>										
Number of swollen and tender joints	x	x	x	x	x	x	x	x	x	x
Morning stiffness	x	x	x	x	x	x	x	x	x	x
Patients Global Assessment	x	x	x	x	x	x	x	x	x	x
Physicians Global Assessment	x	x	x	x	x	x	x	x	x	x
Pain VAS	x	x	x	x	x	x	x	x	x	x
<i><b>Additionally for PsA-patients</b></i>										
BSA of psoriatic skin	x	x	x	x	x	x	x	x	x	x
Nail involvement	x	x	x	x	x	x	x	x	x	x
Dactylitis	x	x	x	x	x	x	x	x	x	x
<b>Health Outcomes</b>										
Hannover Functional Ability Questionnaire (FFbH)	x	x	x	x	x	x	x	x	x	x
EQ-5D	x	x	x	x	x	x	x	x	x	x
Participation at the Etanercept compliance Program	x									





## 7. DATA ANALYSIS/STATISTICAL METHODS

The data collected and statistical methods proposed for analysis in this study will be documented in an NI Statistical Analysis Plan, which will be maintained by the sponsor. This plan will detail the interim analyses as well as the full analysis once the database is complete. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in an NI protocol amendment.

The intention-to-treat population will be used for all effectiveness analyses. It is defined as patients who received at least one dose of Etanercept. Missing values will be assumed to be missing at random and not imputed.

### 7.1 Sample Size Calculation

This is an NI study and as such a formal sample size calculation is not required. However it is planned to enroll ~~1200~~ 1,600 RA and approximately ~~300~~ 400 PsA patients.

The change from baseline in radiographic progression (TSS) in RA subjects from the COMET<sup>1</sup> study based on a combination of MTX and Etanercept was 0.27 (standard deviation of 3.4) indicating that 1200 subjects would have 78% power at the 5% significance level. **Based on experience from different European registries it is expected that from 1.600 patients included into this study around 1.200 will have a complete documentation of the first 18 month (period 1)**

For PsA, the Ravindran paper indicates a mean yearly radiographic progression (modified TSS [mTSS]) of 2.85 with a standard deviation of 5.22. Sample size estimation based on this paper would indicate less than 100 subjects would be required to demonstrate this level of progression at >90% power and at the 5% significance level. It is anticipated that as many as 300 subjects with PsA may be included into the study.

### 7.2 Effectiveness Analysis

The mean changes from baseline in the van der Heijde Sharp Score (TSS) (RA subjects only) will be summarised. The number and percentage of subjects with increase (>0.5), no change (-0.5 to 0.5) or decrease (<-0.5) in TSS will also be presented by visit. Subjects with no change or a decrease can be said to be in Radiographic remission.

The mean changes from baseline in the mTSS (PsA subjects only) will be summarised. The number and percentage of subjects with increase (>0.5), no change (-0.5 to 0.5) or decrease (<-0.5) in mTSS will also be presented by visit.

The change in the VAS from baseline will be summarised by visit.

The relationship between radiographic progression (TSS or mTSS) and disease duration will be assessed via a regression model with progression as the dependent variable and disease duration as the independent variable. Patients with RA and PsA will be analysed separately using data from the baseline visit (pre Etanercept radiograph). Additional

covariates/factors will be considered and documented in the Statistical Analysis Plan. These may include the following:

- Radiographic progression prior to start of Etanercept (historical radiograph)
- Patient's global assessment.
- Pain (VAS).
- Hannover Functional Ability Questionnaire (FFbH).
- Disease activity score (DAS 28) (RA patients).
- BSA (PsA patients).

A paired t-test will be performed on the TSS from before and after Etanercept treatment. The RA and PsA patients will be analysed separately. This will be performed on the TSS score from the pre Etanercept radiograph and the TSS from the 12-18 month radiograph (Visit 5, 6 or 7).

Additionally to the investigation of therapy-induced effects of etanercept treatment on radiographic progression, as revealed by van der Heijde Sharp score, radiographs from 100 RA-patients will be assessed by metacarpal bone mineral density (DXR-BMD), joint space width of metacarpophalangeal joints (JSW-MCP) and proximal interphalangeal (JSW-PIP).

Physician (and Patient) Global Assessment of arthritis will be summarized by visit.

The FFbH will be summarised by visit. The number and percentage of subjects with functional remission will also be presented by visit.

The DAS-28 score (RA subjects only) will be summarized by visit.

BSA (PsA subjects only) will be summarized by visit.

The EQ-5D will be summarized by visit.

Duration of morning stiffness will be summarized by visit.

## 9. ADVERSE EVENT REPORTING

Following section will be added to the description of adverse event reporting:



### **Overdose, misuse, extravasation**

Reports of overdose, misuse, extravasation with the use of a Pfizer product will be recorded on the adverse event page(s) of the case report form, irrespective of the presence of an associated AE/SAE. The investigator must submit reports of overdose, misuse, extravasation to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE

Reports of occupational exposure to a Pfizer product are to be submitted to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE.

## **2. RATIONAL FOR THE EXPANSION OF THE OBSERVATION PERIOD**

Patients with rheumatoid arthritis often suffer from progressing joint destruction. This leads to loss of functionality and a decreased quality of life. If this destruction is not prevented, 25% of these patients will be unable to work after 3 years (1).

As shown in the TEMPO trial, Etanercept inhibits the radiographic progression in combination with MTX and also in monotherapy (2, 3). However there are only a few data for the long-term efficacy of biologics available. As the experience with this ongoing study show that many physicians follow the German recommendations for patients treated with biologics and radiographs are taken frequently, an extension of this study will be a good opportunity to evaluate the long-term effect of Etanercept on radiographic progression in real life.

## **3. RATIONAL FOR THE EXPANSION OF THE PATIENTS INCLUDED**

Data from different European registries show, that around 30% of the patients will stop their treatment within one year. As evaluated for the sample size calculation 1.200 subjects would have 78% power at the 5% significance level for the calculation of the changes of the TSS., Therefore the inclusion of 1.600 patients is required to receive 1.200 completed documentations for the first treatment year

This also implicates the inclusion of around 400 patients with PsA to receive 300 completed documentations from this patient population.

## **4. RATIONAL FOR THE EXPANSION OF THE RECRUITMENT PERIOD**

Since start of the study in March 2012 to end of May 2013 around 1,400 patients have been included. Taking a monthly recruiting rate of 70 – 75 patients into account 8 month will be needed to recruit the last 600 patients. Thus the recruitment will be completed until end of December 2014. This also results in the extension of the overall study period.



## **5. RATIONAL FOR THE ASSESSMENT OF RADIOLOGIC PROGRESSION BY DIGITAL X-RAY RADIOGRAMMETRY (DXR) AND COMPUTER ASSISTED JOINT SPACE ANALYSIS (CAJSA)**

Visualization and assessment of radiological progression of RA is highly important for prognostic purposes. In the clinical routine, radiographic progression is often not sufficiently quantified, since scoring methods used for the subjective evaluation of X-ray images are very time consuming. An efficient, computer-based method may be very useful in addition to the established van der Heijde Sharp score and should improve the quantification of therapeutic effects under treatment with Etanercept.

Digital X-ray Radiogrammetry (DXR) and Computer - Assisted Joint Space Analysis (CAJSA) are two technological methods developed in recent years which can precisely and objectively analyse radiographs as shown in this prospective and retrospective study design. Two relevant parameters of radiological progression – the metacarpal bone mineral density (DXR - BMD) and joint space width – are used to detect the course of the disease (3, 4, 5, 6). Periarticular bone mineral density loss also shows a high association with RA disease activity (7). A retrospective trial shows that these two methods are able to demonstrate differences between drug therapies, even at small doses (8, 9). Both techniques and their parameters optimize the findings of radiographic progression in comparison to established scoring systems (10). A precise assessment of periarticular demineralization and RA-related reduction of joint space widths using DXR and CAJSA in patients undergoing Etanercept treatment highlight the effectivity of this innovative therapy strategy.

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